

CALIFORNIA ENVIRONMENTAL PROTECTION AGENCY
DEPARTMENT OF PESTICIDE REGULATION
MEDICAL TOXICOLOGY BRANCH

SUMMARY OF TOXICOLOGY DATA

Tebuconazole

Chemical Code # 3850, Tolerance # 51951
SB 950 # New A.I.

March 28, 2003

I. DATA GAP STATUS

Chronic toxicity, rat:	No data gap, no adverse effect
Chronic toxicity, dog:	No data gap, no adverse effect
Oncogenicity, rat:	No data gap, no adverse effect
Oncogenicity, mouse:	No data gap, no adverse effect
Reproduction, rat:	No data gap, no adverse effect
Teratology, rat:	No data gap, possible adverse effect indicated
Teratology, rabbit:	No data gap, possible adverse effect indicated
Gene mutation:	No data gap, no adverse effect
Chromosome effects:	No data gap, no adverse effect
DNA damage:	No data gap, no adverse effect
Neurotoxicity:	No data gap, no adverse effect

Toxicology one-liners are attached.

All record numbers through 161055 were examined.

** indicates an acceptable study.

Bold face indicates a possible adverse effect.

indicates a study on file but not yet reviewed.

File name: T030328

Revised by Thomas Moore, 3/28/03

II. TOXICOLOGY ONE-LINERS AND CONCLUSIONS

These pages contain summaries only. Individual worksheets may contain additional effects.

COMBINED, RAT

** 083, 084, 085; 145048, 144773, 144782; "HWG 1608: Study for Chronic Toxicity and Cancerogenicity in Wistar Rats (Administration in Diet for Two Years)"; (E. Bomhard and W. Ramm; Bayer AG, Toxicology Division, Federal Republic of Germany; Study No. 96711, 96711-1, 96711-3; 1/25/88, supp. 5/7/93; HWG 1608 (purity: 94.7 to 96.9%) was administered in the diet of 50 rats/sex/group at concentrations of 0, 100, 300, or 1000 ppm for 2 years (test material consumption: (M) 0, 5.3, 15.9, or 55.0 mg/kg/day, (F) 0, 7.4, 22.8, or 86.3 mg/kg/day). An additional 10 rats/sex/group were retained as a satellite group for an interim necropsy after 12 months of treatment. The percent survival after 2 years for the males was 82, 86, 84, and 94%, respectively and for the females, 80, 76, 80, and 84%, respectively. The mean body weight of the 1000 ppm females was lower than the control value throughout the study ($p < 0.01$, 7.7% reduction after 101 weeks of treatment). Increased incidences of pigmentation of the Kupffer cells in the liver and hemosiderin in the spleen was noted in the 1000 ppm females. However, no related effects were noted in the hematological parameters. Although the mean adrenal weight was reduced in a dose-related manner in the females, the increased incidence of hemorrhagic degeneration in the cortex of the adrenal in the control rats may have contributed to the actual weight differential observed. Although a dose-related effect was noted in the incidence of total thyroid tumors in the males (0, 3, 3, and 6, respectively), the highest incidence of 12% was within the percentage range observed for the historical control data. NOEL: (M) 1000 ppm (55.0 mg/kg/day); (F) 300 ppm (22.8 mg/kg/day) (based upon increased incidence of hemosiderin in the spleen and lower mean body weight in the 1000 ppm group); NOAEL: 1000 ppm; **Oncogenicity not indicated; Study acceptable.** (Moore, 10/21/96)

CHRONIC TOXICITY, RAT

See Combined Rat above.

CHRONIC TOXICITY, DOG

** 081, 082; 145044, 145046; "Safety Evaluation of HWG 1608: Chronic (1 Year) Feeding Study in Dogs"; (M.C. Porter, et. al.; Miles Inc., Toxicology Department, Elkhart, IN; Report Nos. 99673, 99673-1; 6/28/89, 10/5/92); HWG 1608 (purity: 96%) was administered in the diet of 4 dogs/sex/group at concentrations of 0, 100 or 150 ppm for one year (test material consumption: (M) 0, 2.96, 4.39 mg/kg/day, (F) 0, 2.94, 4.45 mg/kg/day). No treatment-related mortality resulted. No treatment-related effects upon clinical observations, hematology, clinical chemistry or ophthalmology evident. Only treatment-related effect reported was hypertrophy of the zona fasciculata in the adrenal glands of the 150 ppm treatment group (all eight animals in the high dose group in contrast to one animal in the control and none in the 100 ppm group). **No adverse effect indicated.** NOEL (M/F): 100 ppm (M: 2.96 mg/kg/day, F: 2.94 mg/kg/day) (based upon the incidence of hypertrophy in the adrenal glands); NOAEL: 150 ppm; **Study acceptable.** (Moore, 10/10/96)

** 080; 145041; "HWG 1608: Study of Chronic Toxicity to Dogs after Oral Administration (twelve-month feeding study)"; (E. von Keutz; Bayer AG, Institute of Toxicology, Federal Republic of Germany; Study No. 95690; 11/11/87); HWG 1608 (purity: 96.9%) was administered in the feed of 4 dogs/sex/group at concentrations of 0, 40, or 200 ppm for 52 weeks or 1000 ppm for 39 weeks followed by 13 weeks at 2000 ppm (calculated test material consumption: (M)-0, 1.36, 7.22, 36.0 for 39 weeks and 68.7 mg/kg/day for 13 weeks, (F)-0, 1.43, 7.51, 38.8 for 39 weeks and 73.1 mg/kg/day for 13 weeks). Body weight and clinical observation data did not reflect any treatment-related effects. In the ophthalmological examination, 2 dogs in the 200 ppm treatment group exhibited alterations of the lens (central stellar opacities) by the 32nd week which persisted to the termination of the study. Another dog in the 1000/2000 ppm treatment group was noted to have the same lesion by the 26th week, but it was no longer evident in the 39th week. Minimal effects

upon the liver were noted with an increase in the serum alkaline phosphatase and liver N-demethylase activities (1000/2000 ppm group-maximal response of 189 and 199%, respectively in the females at 52 weeks). Liver triglyceride levels were up slightly after 52 weeks of treatment in the 1000/2000 ppm group (males-120%, females-161%). Heightened lobulation of the liver was noted in 2 dogs of the 200 ppm group and in 5 dogs in the 1000/2000 ppm group. **No adverse effect indicated.** NOEL (M/F): 40 ppm (based upon a possible treatment-related effect upon the eyes of the dogs in the 200 ppm group), NOAEL: 1000 ppm. **Study acceptable.** (Moore, 10/4/96)

Collectively, both studies contain sufficient information to satisfy the current guidelines for an acceptable chronic oral toxicity study in dogs.

ONCOGENICITY, RAT

See Combined Rat above.

ONCOGENICITY, MOUSE

** 086; 144785; "HWG 1608: Study for Cancerogenicity in NMRI Mice (Administration in Diet for up to 21 Months)"; (E. Bomhard and W. Ramm; Bayer AG, Toxicology Division, Federal Republic of Germany; Study No. 96709; 1/25/88); 1608 HWG (purity: 94.7 to 96.9%) was administered in the feed of 50 mice/sex/group at doses of 0, 20, 60 or 180 ppm for 21 months (test compound consumption: (M) 0, 5.9, 18.2, 53.1 mg/kg/day, (F) 0, 9.0, 26.1, 80.5 mg/kg/day, respectively). An additional 10 animals/sex/group were retained as a satellite group for an interim necropsy after 12 months of treatment. There were no apparent treatment-related effects upon mortality, body weights, clinical weights or hematology. Mean total bilirubin levels were increased in the females at 180 ppm after 12 months and at 20, 60 and 180 ppm after 21 months. Liver was the considered target organ with minimal signs of vacuolation and lipid deposition in the mid and high dose group over the course of the study. No indication of oncogenicity was noted. NOEL (M/F): 20 ppm (M: 5.9 mg/kg/day, F: 9.0 mg/kg/day) (based upon vacuolation and lipid deposition in the liver of the 60 ppm treatment group; NOAEL: 180 ppm; **No oncogenicity indicated. Study acceptable.** (Moore, 10/24/96)

087, 088, 089; 144788, 144790, 144791; "HWG 1608: Toxic Dose Range Carcinogenicity Study in NMRI Mice (Supplement to Study T 6018953 - Carcinogenicity in NMRI Mice with Administration in Diet over a 21-Month Period)"; (E. Bomhard and R. Burnett; Bayer AG, Depart. of Toxicology, D-56 Wuppertal 1, F.R. Germany; Study No. 96709-3, 96709-4, 96709-5; 12/12/91); HWG 1608 (purity: 96.2%) was administered in the diet of 50 mice/sex/group at doses of 0, 500, or 1500 ppm for 21 months (test compound consumption: (M) 0, 84.9, 279.0 mg/kg/day, (F) 0, 103.1, 356.5 mg/kg/day). An additional 10 mice/sex/group were retained as a satellite group for an interim necropsy after 12 months of treatment. No treatment-related increase in mortality noted. A delay in body weight gain in the high dose group was evident. Liver was the target organ with an increase in organ weight and increases in levels of serum enzymes (500 and 1500 ppm, $p < 0.01$). Histologically, increased numbers of animals with lesions in the liver were noted for both treatment groups in a dose-response manner. Incidences of liver adenomas and carcinomas were significantly increased in the 1500 ppm treatment group (adenoma: 0 (M) 3/47, (F) 0/47, 1500 (M) 17/48, (F) 2/46; carcinoma: 0 (M) 0/47, (F) 1/47, 1500 (M) 10/48, (F) 12/46). Chronic NOEL: (M/F) < 500 ppm (based upon histopathological effects on the liver); Increased incidence of liver adenomas and carcinomas in the 1500 ppm group were not considered to be an adverse effect because the dose levels exceeded the MTD. **Study Supplemental.** (Moore, 10/28/96)

REPRODUCTION, RAT

** 094; 144803; "HWG 1608: Two-Generation Study in Rats"; (R. Eiben; Bayer AG, Toxicology Division, Federal Republic of Germany; Report No. 91064; 11/12/87); HWG-1608 (purity: 95.2%) was administered in the diet of 25 rats/sex/group at doses of 0, 100, 300 or 1000 ppm for two generations in which two litters were produced in each generation. The F0 generation received

the diet for 17 weeks prior to the first mating and the F1B generation received the diet for approximately 10 weeks after weaning until the first mating. No treatment-related deaths or clinical signs were noted in the adults. The mean body weights of both the F0 and F1B adults in the 1000 ppm group were lower than the control means. The mean litter size of both litters (F1A and F1B) in the 1000 ppm F0 group were less than that the control. Mean pup weights of the F1A and F1B litters in the 1000 ppm group were less than the control values over the lactation period. The viability and lactation indices for the F1A and F1B pups in the 1000 ppm group were less than those of the control pups. **No adverse effect indicated. Parental NOEL:** (M/F) 300 ppm (based upon lower mean body weights of the 1000 ppm treatment group; **Reproductive NOEL:** 300 ppm (based upon reduced litter size of the F1A and F1B litters in the 1000 ppm treatment group); **Developmental NOEL:** 300 ppm (based upon lower mean body weights and lower viability and lactation indices of the F1A and F1B litters in the 1000 ppm treatment group); Test material intake during premating period for the 300 ppm dose level varied from 21.6 to 27.8 mg/kg/day for the F0 generation and 27.1 to 33.9 mg/kg/day for the F1B generation; NOAEL: 1000 ppm.; **Study acceptable.** (Moore, 12/17/96)

TERATOLOGY, RAT

****072; 145020;** "Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Rat" (H. Becker, *et al*; Research and Consulting Company AG, Itingen, Switzerland; Sponsor Report No. 96756; 4/28/88); HWG 1608 Technical (Batch No. 16002/85; 98.3% a.i.), dosed as a suspension in aqueous 0.5% Cremophor EL; groups of 25 mated female Wistar/HAN, Kfm:WIST(SPF) rats were treated with 0 (vehicle), 30, 60, or 120 mg/kg on days 6-15 of gestation; reduced food consumption and increased liver weight was observed in the mid-and high-dose group between days 6 and 16 of gestation; however, reduced maternal weights were only observed at the high dose from days 7 to 21 of gestation; also, increased resorptions were reported in the high-dose group which is related to the increased incidence of black/brown fluid found in the uterus; in fetuses, high-dose group showed reduced body weight and one incident each of missing tail and malformed face (agnathia, microstomia, anophthalmia); **possible adverse effect:** resorptions; maternal NOEL = 30 mg/kg/day (increased absolute and relative liver weight); developmental NOEL = 60 mg/kg/day (increased resorption); **Acceptable.** (Duncan, 12/17/96)

**** 075; 145031;** "HWG 1608: Study for Embryotoxic Effects on Rats After Dermal Administration" (M. Renhof; Bayer AG, Institute of Toxicology, FRG; Sponsor Report No. 98359; 8/30/88); HWG 1608 (Batch No. 16012/86; 97.4% a.i.), suspended in 1% Cremophor EL and applied at concentrations of 5% (low), 15% (mid), or 50% (high) to groups of 25 mated female Wistar, Bor:WISW(SPF) rats at dose levels of 0 (vehicle), 100, 300, and 1000 mg/kg for 6 h/day on days 6-15 of gestation; no significant toxicity was observed in dams and no developmental toxicity was observed in litters or fetuses; **no adverse effects;** maternal NOEL = 1000 mg/kg/day (no effects at HTD); developmental NOEL = 1000 mg/kg/day (no effects at HTD); **Acceptable.** (Duncan, 12/20/96)

TERATOLOGY, RABBIT

****092; 144799;** "Embryotoxicity (Including Teratogenicity) Study with HWG 1608 Technical in the Rabbit" (H. Becker, *et al*; Research and Consulting Company AG, Itingen, Switzerland; Sponsor Report No. 96764; 2/26/88); HWG 1608 Technical (Batch No. 16002/85; 98.2% a.i.), suspended in 0.5% Cremophor EL; groups of 16 mated female Chinchilla rabbits (Kfm:CHIN, SPF) were treated with 0 (vehicle), 10, 30, or 100 mg/kg on days 6-18 of gestation; one death at 100 mg/kg/day, apparently from misdosing; reduced food consumption (Day 6-19) and weight gain (Day 6-28) in dams and increased rate of resorptions at 100 mg/kg; 7/124 fetuses (5/14 litters) in 100 mg/kg/day group had major malformations (five of these had peromelia affecting the foreleg); **possible adverse effect:** resorptions, peromelia; maternal NOEL = 30 mg/kg/day (based on decreased food consumption and weight gain at 100 mg/kg/day); developmental NOEL = NOAEL = 30 mg/kg/day (based on increased resorptions and increased number of fetuses with peromelia at 100 mg/kg/day); **Acceptable.** (Duncan, 1/9/96)

****093; 144801;** " HWG 1608 Technical (c.n. Tebuconazole)/ Embryotoxicity Study (Including Teratogenicity) and Supplemental Investigations on the Maternal Toxicity in Pregnant Rabbits" (H. Becker and K. Biedermann, Research and Consulting Company AG, Itingen, Switzerland; Sponsor Report No.106899; 5/31/95); HWG 1608 Technical (Batch No. 816196048; 96.30-96.80% a.i.), suspended in 0.5% Cremophor EL; groups of 16 mated female Chinchilla rabbits (Kfm:CHIN, SPF) were treated with 0 (vehicle), 10, 30, or 100 mg/kg on days 6-18 of gestation; a supplemental toxicity study in groups 5 dams at the same dose levels showed single-cell hepatic necrosis in all treatment groups; in the definitive study there was one death at 10 mg/kg/day; reduced food consumption and weight gain (Day 6-19) in dams and increased embryonic resorptions at 100 mg/kg; malformations were observed in 5/14 litters in each of the 30 and 100 mg/kg/day groups (5/109 and 5/119 fetuses, respectively); there was no pattern in the types of malformations observed; **possible adverse effect:** resorptions, malformations; maternal NOEL < 10 mg/kg/day (based on hepatic necrosis in suppl. study); developmental NOEL = NOAEL = 10 mg/kg/day (based on increased resorptions and incidence of fetal malformations at 30 and 100 mg/kg/day); **Acceptable.** (Duncan, 1/27/97)

TERATOLOGY, MOUSE

****077, 078; 145034, 145035;** AHWG 1608 Study of Embryotoxic Effects on Mice after Oral Administration@ (M. Renhof, Bayer AG, Institute of Toxicology/Agriculture, FRG, Project ID # 97411, 3/14/88). HWG 1608 Technical (Batch 1616002/84, 93.6% purity) was administered by oral gavage to 25 mated NMRI mice/dose from days 6 through 15 of gestation at 0, 10, 30, and 100 mg/kg/day. An additional 10 mated mice/dose treated at 0, 10, 20, 30, and 100 mg/kg/day were allocated for histopathology and clinical chemistry. No unscheduled deaths were reported. Histopathology revealed cytoplasmic vacuoles in liver cells of all animals from the 100 mg/kg group as well as increased fat content and triglyceride concentrations. Elevated liver enzymes were detected at 10 mg/kg (ALT) and at 30 mg/kg (ALT and AST). **Possible adverse effects indicated:** Increased incidence of cleft palate (4/20 litters vs. 1/24 litters, P < 0.05) were observed at the high dose group as compared to the control group. Stunted fetuses or runts were found in groups treated at 30 mg/kg and higher. Maternal NOEL < 10 mg/kg/day (based on elevated ALT); developmental NOEL = NOAEL = 10 mg/kg/day (based on stunted fetuses); **unacceptable but possibly upgradeable** with submission of food consumption data and frequency and duration of clinical observations; (Leung, 1/22/97).

****079; 145037; A** Embryotoxicity Study (Including Teratogenicity) and Supplementary Embryotoxicity Study (Including Teratogenicity) in the Mouse@ (H. Becker et. al., Embryo toxicity Study (Including Teratogenicity) and Supplementary Embryotoxicity Study (Including Teratogenicity) in the Mouse, Project#s 319432 and 360270, 5/31/95). HWG 1608 technical (Batch # 816196048, 95.8 -96.8% purity) was administered via oral gavage to pregnant NMRI-HAN mice from days 6 through 15 of gestation. 1st (0, 10, 30, or 100 mg/kg/day) and 2nd (0, 1, or 3 mg/kg/day) main studies consisted of 35 and 10 dams/dose, respectively. Additional subgroups of 30 and 7 dams/dose, respectively, were used to assess histopathology and clinical chemistry. No signs of treatment-related deaths, maternal body weights or food consumption were evident. Gross necropsy revealed increased relative liver weights and elevated cytochrome p450 content and N-and O-demethylase activities were reported in dams treated at the 30 and 100 mg/kg/day dose levels. Histopathological exam indicated increased incidences and severity of vacuolization of the liver at 10, 30, and 100 mg/kg/day. **Possible adverse effects:** The ratio (%) of postimplantation loss (resorption) to implantation sites was significantly increased at 30 and 100 mg/kg/day. Furthermore, high litter incidences of cleft palate, exencephaly and acrania (partial) were detected at 100 mg/kg during fetal examination. Maternal NOEL = 3 mg/kg/day (based on abnormal liver histology), developmental NOEL = NOAEL = 10 mg/kg/day (based on resorption). **Acceptable.** (Leung, 1/17/97).

****090; 144793;** A Embryotoxicity Study (Including Teratogenicity) with HWG 1608 Technical in the Mouse (Dermal Application)@ (H. Becker, et. Al., Research and Consulting Company (RCC) AG, Itingen, Switzerland, Report # 101262, 7/16/90). HWG 1608 Technical (Batch # 16002/85, 98.1% purity for main study, Batch # 816896061, 96.9% for supplemental study) was applied

dermally 6 hours/day to 25 mated NMRI/HAN mice/dose at 0 (4% aqueous CMC), 100, 300, or 1000 mg/kg from days 6 through 15 of gestation. An additional 10 mated mice/dose were allocated for histological exam and clinical chemistry. No unscheduled deaths, clinical signs, or local skin reactions related to treatment with HWG 1608 technical were reported in pregnant mice. Histopathological exam revealed hepatocellular fatty change of the periportal areas in 8 mice in the mid dose and all mice in the high dose groups. Increased cytochrome p450 content, and N-demethylase and O-demethylase activities were detected in liver tissues from mid and high dose mice. **Possible adverse effects:** increased fetal incidence of cleft palate and supernumerary ribs were observed in fetuses at 1000 mg/kg/day. Maternal NOEL = 100 mg/kg/day (based on abnormal liver histopathology and elevated hepatic cyto p450 and enzymes), developmental NOEL = NOAEL = 300 mg/kg/day (based on increased frequency of cleft palate and supernumerary ribs). **Acceptable.** (Leung, 1/15/97).

GENE MUTATION

095, -096; 144804, 144805; "Salmonella/Microsome Test to Evaluate for Point Mutagenic Effects" (Author: Herbold, B. A.; Bayer AG, Toxicology Division, FRG; Sponsor Report Nos. 91068; 1/27/88; Addendum I dated 2/8/88); 842; HWG 1608 (Batch No. 1616001/86; 96.6% a.i.), dissolved in DMSO; *Salmonella typhimurium* strains TA98, TA100, TA1535, TA1537, TA1538 with and without activation (Aroclor 1254-induced rat liver S9 fraction), by plate incorporation; 0 (DMSO), 37.5, 75, 150, 300, 600, 1200, 2400 ug/plate (first trial; did not include TA1538) and 0 (DMSO), 39.5, 59.3, 88.9, 133.3, 200, 300, 450 ug/plate (second trial); 4 plates/strain/dose level; 48 hr incubation; results were confirmed in a limited (TA98, TA100, TA1535, TA1537) or complete (TA1538) trial; **no adverse effects; cytotoxicity at doses of approx. 60-300 ug/plate and above; no increase in reversion rates; positive controls were functional; **Acceptable.** (Duncan, 9/6/96)

097; 144807; "Mutagenicity Study for the Detection of Induced Forward Mutations in the CHO-HGPRT Assay In Vitro" (Author: Lehn, H.; Bayer AG, Toxicology Division, FRG; Sponsor Report No. 87318; 5/31/88); 842; HWG 1608 (Batch No. 1616001/86; 96.6% a.i.), dissolved in DMSO; CHO-K1-BH4 cells; 80, 90, 92.5, 95, 97.5, 100 ug/ml in non-activated cultures and 12.5, 25, 50, 100, 150, 200 ug/ml in activated (Aroclor 1254-induced rat liver S9 fraction) cultures with appropriate negative and positive controls; two trials with one culture/dose level and one trial with two cultures/dose level; 2 hr exposure; **no adverse effects; no significant increases in mutation frequency were observed; **Acceptable.** (Duncan, 9/6/96)

CHROMOSOME EFFECTS

098; 144811; "In Vitro Cytogenetic Study with Human Lymphocytes for the Detection of Induced Clastogenic Effects" (Author: Herbold, B. A.; Bayer AG, Toxicology Division, FRG; Sponsor Report No. 95694; 2/2/88); 843; HWG 1608 (Batch No. 1616001/86; 96.6% a.i.), dissolved in DMSO; human lymphocytes cultured from one male and one female donor; 3, 10, 30 ug/ml in non-activated cultures and 30, 100, 300 ug/ml in activated (Aroclor 1254-induced rat liver S9 fraction) cultures with appropriate negative and positive controls; one trial with two cultures/dose level; exposure: 21 hours without S9 and 2.5 hours with S9; **no adverse effects; no significant increases in frequency of chromosomal aberrations were observed; **Acceptable.** (Duncan, 9/6/96)

099; 144813; "Sister Chromatid Exchange Assay in Chinese Hamster Ovary (CHO) Cells" (Author: Putman, D. L. ; Microbiological Associates, Bethesda, MD; Sponsor Report No. 94858; 9/3/87); 843; HWG 1608 (Batch No. 1616001/86; 96.5% a.i.), dissolved in DMSO; 0 (culture medium), 0 (DMSO), 4, 8, 15, 30 ug/ml for 30 h exposure in non-activated cultures and 0 (culture medium), 0 (DMSO), 15, 30, 60 120 ug/ml for 2 h exposure in activated (Aroclor 1254-induced rat liver S9 fraction) cultures; one trial with duplicate cultures at each dose level; 25 cells/replicate/treatment were examined for SCEs; **no adverse effects; no significant increases in frequency of SCEs were observed; no metaphases examined at 120 ug/ml w/activation due to cytotoxicity; CP and TEM were functional; **Acceptable.** (Duncan, 9/19/96)

100; 144814; "Dominant Lethal Test on the Male Mouse to Evaluate for Mutagenic Effect" (Author: Herbold, B.; Bayer AG, Toxicology Division, FRG; Sponsor Report No. 94404; 8/20/86); 843; HWG 1608 (Batch No. 16007/83; 93.5% a.i.); dosed as 200 mg/ml mixture in 1% Cremophor; 0 (vehicle), 2000 mg/kg; 50 male Bor:NMRI mice/dose group; each male was mated to 12 untreated females during the 48 d following dosing (mating period was 4 d); no positive control; **no adverse effects; no dominant lethal effect; lack of functional positive control; **Not acceptable** but upgradeable with submission of positive control data from a dominant lethal test performed in the same lab and approximate time period as the current study. (Duncan, 9/24/96)

DNA DAMAGE

101; 144817; "Micronucleus Test on the Mouse to Evaluate for Mutagenic Effect" (Author: Herbold, B.; Bayer AG, Toxicology Division, FRG; Sponsor Report No. 94529; 1/4/85); 843; HWG 1608 (Batch No. 16007/83; 95.3% a.i.), dosed as a mixture in 1% Cremophor; single doses of 0 (vehicle), 200, 500, or 2000 mg/kg to groups 5 Bor:NMRI mice/sex with bone marrow collection at times of 24, 48, and/or 72 h; 1000 polychromatic and 1000 normochromatic erythrocytes/-animal were examined for the presence of micronuclei; **no adverse effects were observed; inhibition of erythropoiesis was observed at all dose levels; no increase in micronucleated erythrocytes was observed; cyclophosphamide was functional in the assay. **Acceptable**. (Duncan, 9/26/96)

102; 144819; "Mutagenicity Test on HWG 1608 Techn. In the Rat Primary Hepatocyte Unscheduled DNA Synthesis Assay" (Author: Cifone, Maria A.; Hazleton Laboratories America, Inc., Kensington, MD; Sponsor Report No. 94988; 8/10/88, amended report); 844; HWG 1608 (Batch No. 1616001/86; 96.5% a.i.), dissolved in DMSO; primary hepatocyte cultures from male Fisher 344 rat were exposed to 0 (DMSO), 0.504, 1.01, 2.52, 5.04, 10.1, or 25.2 ug/ml for 18 h; DNA synthesis was measured by ³H-thymidine incorporation followed by autoradiography; three replicate cultures/dose level, single trial; nuclear grains were counted in 50 cells/culture (150/treatment); **no adverse effects** were observed; no increase in net nuclear grain counts was observed; complete cytotoxicity was observed at doses above 25.2 ug/ml; 2-AAF was functional in the assay; **unacceptable, but possibly upgradeable** with the submission of individual net nuclear grain counts/cell. (Duncan, 9/26/96)

103; 144821; "HWG 1608 Pol Test on E. Coli to Evaluate for Harmful Effects on DNA" (Author: Herbold, B.; Bayer AG, Toxicology Division, FRG; Sponsor Report No. 94556; 7/1/83); 844; HWG 1608 (Batch No. 16001/83; 97.1% a.i.), dissolved in DMSO, was tested in *E. coli* strains (K 12)p 3478 and W 3110 at doses of 0 (DMSO), 625, 1250, 2500, 5000, and 10000 ug/plate, with and without a metabolic activation system (Aroclor 1254-induced rat S9 liver homogenate fraction) for 24 hrs in a disk diffusion assay; a single trial with four replicates/treatment was conducted; **no adverse effects** were observed; no differential increase in growth inhibition zone was observed; no cytotoxicity; MMS and chloramphenicol were functional; **Unacceptable** and cannot be upgraded because an activation-dependent positive control was not tested. (Duncan, 10/1/96)

NEUROTOXICITY

223; 159040; "An Acute Oral Neurotoxicity Screening Study with Technical Grade Tebuconazole (Folicur®) in Fischer 344 Rats" (Sheets, L.P. and Gilmore, R.G., Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS, Study No. 96-412-JI, Report No. 107782, 12/8/97). 818. Technical Grade Tebuconazole (Folicur) (Batch No. 603-0013, purity=96.5%), prepared in 0.5% methylcellulose/0.4% Tween 80 in deionized water, was administered by gavage in a single dose at concentrations of 0 (vehicle), 100, 250 (females only), 500, and 1000 (males only) mg/kg to 12 Fischer 344 CDF(F-344)/BR rats per sex per dose level. 6 males at 1000 mg/kg and 1 male at 500 mg/kg died during the study. Treatment-related ataxia, body cool to touch, lacrimation, decreased activity, and oral, nasal (red), and urine staining at the mid and high dose levels were observed with all signs clearing in the survivors after day 3. For the FOB, treatment-related effects of incoordination (both home cage and open field), diminished approach and touch response reflexes, and decreased mean body temperature at the mid and high dose levels in both males and females, yellow perianal staining during handling and diminished righting reflex at the

high dose level in males and females, diminished auditory and tail pinch response reflexes and decreased mean hindlimb grip strength at the mid and high dose levels in males, and decreased mean hind limb strength at the high dose level and decreased mean footsplay at all dose levels in females were observed at Day 0 with all effects clearing by Day 7 except for footsplay that cleared by Day 14. Statistically significant increased motor activity at 100 mg/kg was observed in both males and females at Day 0 clearing by Day 14. Micropathological examination revealed no compound-related lesions in the high dose males or females. **No adverse effects.** NOEL (M/F)<100 mg/kg (based on increased motor activity). **Acceptable.** (Corlett, 2/10/98)

224; 161055; "**Original:** An Acute Oral Neurotoxicity Screening Study with Technical Grade Tebuconazole (Folicur®) in Fischer 344 Rats; **Supplemental:** A Special Acute Oral Neurotoxicity Study to Establish a No-Observed-Effect Level with Technical Grade Tebuconazole in Fischer 344 Rats" (Sheets, L.P., Bayer Corporation, Agriculture Division, Toxicology, Stilwell, KS, Study No. 97-912-LZ, Report No. 107782-1, 4/9/98). Technical Grade Tebuconazole (Batch No. 603-0013, purity=96.2-97.3%), suspended in 0.5% methylcellulose/0.4% Tween 80 in deionized water, was administered by gavage in a single dose at concentrations of 0 (vehicle), 20, or 50 mg/kg to 12 Fischer 344 CDF(F-344)/BR rats per sex per dose level. No animals died during the study. No treatment-related clinical signs were observed. No treatment-related effects were observed during FOB assessments. No statistically significant effects were observed during motor activity assessments. **No adverse effects.** NOEL (M/F)=50 mg/kg (based on FOB and motor activity assessments). **Supplemental study** (only 2 dose levels were used, no neuropathology on the test animals was performed, no analysis of the dosing material was submitted, and activity testing was conducted only at day 0). (Corlett, 6/4/98)

Summary: Additional data were submitted as an adverse effects disclosure report to supplement an acute oral neurotoxicity study with rats to establish an overall no-observed-effect level for tebuconazole based on FOB and motor activity. Since compound-related effects on motor and locomotor activities at higher dose levels (100 mg/kg and higher) in the original study (record # 159040) had cleared by day 7, recovery at lower dose levels in the supplemental study was not examined. The original study indicated a NOEL < 100 mg/kg based on increased motor activity. No evidence of compound-related lesions in high dose (\geq 100 mg/kg) animals were observed or reported during micropathological examination. Collectively, data from both studies support an overall NOEL of 50 mg/kg based on FOB and motor activity.

METABOLISM STUDIES

** 104,-105; 144823, 144854; "FOLICUR: Metabolism Part of the General Metabolism Study in the Rat"; (W. Ecker, et. al.; BAYER AG, Institute of Metabolism Research, Monheim, Federal Republic of Germany; Report No. 97438; 12/21/87); [Phenyl-UL-14C] HWG 1608 (specific activity: 84.4 mCi/mg; radiochemical purity: > 99%) was administered to 5 rats/sex/group at single doses of 2 or 20 mg/kg or after repeated dosing of 2 mg/kg with nonradiolabeled test material for 14 days, a single dose of labelled material at 2 mg/kg. [Triazole-3,5-14C] HWG 1608 (specific activity: 56.5 mCi/mg; radiochemical purity-98.4%) was administered to 5 rats/sex at a single dose of 20 mg/kg. Radiolabeled material was assayed in the urine, and feces of all groups for up to 72 hours. The chemical structures of specific radiolabeled metabolites were identified. Females showed a higher renal elimination rate than males (26 to 35% vs. 15 to 18%, respectively). Conversely, males exhibited a higher portion of excreted radioactivity in the feces (77 to 80% vs. 60 to 67%, respectively). Among the metabolites identified, oxidation of the #5 carbon of the pentane chain to an alcohol and then to a carboxyl group was the primary pathway. These metabolites were then further conjugated together sulfate or glucuronide. The metabolic profile was altered at the higher dose level with a shift to a greater percentage of the alcohol in comparison to the carboxyl containing metabolite. The treatment with the labeled triazole moiety resulted in largely the same metabolic profile except for the recovery of labeled triazole in the urine. Study **acceptable.** (Moore, 11/20/96)

** 106, 107; 144856, 144857; "[Phenyl-U-14C] HWG 1608: Study of Biokinetic Behavior in the Rat"; (H. Weber; BAYER AG, Institute of Metabolism Research, Monheim, Federal Republic of

Germany; Report No. 97439, 97439-1; 10/6/87); [Phenyl-U-14C] HWG 1608 (specific activity: 84.4 mCi/mg; radiochemical purity:> 99%) was administered to 5 rats/sex/group at single doses of 2 or 20 mg/kg or after repeated dosing of 2 mg/kg with nonradiolabeled test material for 14 days, a single dose of labeled material at 2 mg/kg. Radiolabeled material was assayed in the plasma, urine, and feces of all groups and in the bile and expired CO₂ of one group each. Maximum relative plasma concentrations ranged from 0.11 to 0.20 and were achieved 0.33 to 1.7 hours after administration of the test material. After 72 hours, % excreted ranged from 91 to 98%. A difference in sex-related excretion of the test material was noted with males having a urine/feces ratio of 16/78 in contrast to the females which excreted at a ratio of 30/62. Biliary excretion was only measured in males. Ninety percent of the radiolabel was recovered in the bile after a single pass through the liver. Only 0.03% of the radiolabel was recovered in the expired air. Residual label in the tissues (excluding the gastrointestinal tract) ranged from 0.21 to 0.67% of the administered dose after 72 hours. Study **acceptable**. (Moore, 11/4/96)

SUBCHRONIC STUDIES

** 063, 064; 144986, 144987; "HWG 1608: Subchronic Toxicological Study with Rats, Feeding for 13 Weeks"; (E. Bomhard and B. Schilde; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany; Study Nos. 94212, 94212-1; 10/27/86, 9/29/87); HWG 1608 (purity: 93.4%, symmetrical isomer: 4.8%) was administered in the diet to 10 rats/sex/group for 13 weeks at concentrations of 0, 100, 400, or 1600 ppm (test material consumption: (M) 0, 8.6, 34.8, or 171.7 mg/kg/day, (F) 0, 10.8, 46.5, 235.2 mg/kg/day). One male and one female in the 1600 ppm group died during the study. The mean body weights of the 1600 ppm animals were reduced (88.4 to 91.9% of control, p<0.05) with increased food consumption. No apparent treatment-related effects were noted for hematology and ophthalmology. Liver N-demethylase activity and cytochrome P450 content were increased in the 1600 ppm males (p<0.01). Vacuoles were noted in the adrenal zona fasciculata of females of the 400 and 1600 ppm groups and in the 1600 ppm males. Splenic hemosiderosis was evident in the high dose females. Dose relationship of splenic effects were less determined in the males. Target organs: spleen and adrenals; **No adverse effects** indicated. NOEL: (M) 400 ppm, (F) 100 ppm (based upon effect on adrenals in the 400 ppm group females and the 1600 ppm group males); NOAEL: 1600 ppm. Study **acceptable**. (Moore, 10/11/96)<

065; 144989; "HWG 1608: Study of the Subacute Oral Toxicity to Rats"; (K.G. Heimann and G. Kaliner; Study No. 94531; 11/12/84); HWG 1608 (purity: 97.0%) was administered by gavage daily for 4 weeks to 20 rats/sex/group at doses of 0, 30, 100, or 300 mg/kg/day. Ten animals/sex/group were held for an additional 4 weeks of a recovery period. No treatment-related deaths apparently occurred. Mean body weights of the 300 mg/kg animals were reduced during the 4th week and recovered by the end of the study. Reduced hemoglobin content was noted in the 300 mg/kg males (p<0.05) and in both the 100 and 300 mg/kg females (p<0.01) at the end of the treatment period. Concomitant reduction in the hematocrit occurred. An increase in leucocyte number in the 300 mg/kg females (p<0.01) was evident as well. No differences were noted at the end of the recovery period. Although serum enzymes were elevated in the high dose females at the end of the treatment period (p<0.01), the levels had returned to those of the controls by the end of the recovery period. Likewise, the liver enzyme activity levels and triglyceride content which were elevated in the high dose animals after treatment, had returned to control levels during the recovery period. The spleen, liver and adrenals were target organs. Sclerosis of the red pulp of the spleen was associated with a decrease in iron content and atrophied splenic follicles (300 mg/kg females). In the liver of these females, an increase in the periportal stroma was noted. Bile duct proliferation was evident and fatty droplets were observed in the hepatocytes. In the males, a fatty change was noted in the hepatocytes with the centrilobular hepatocytes being enlarged. In the adrenals of the high dose females, cells of the zona fasciculata were irregularly arranged and contained fat vacuoles. After the 4 week recovery period, an increase in the fiber content of the red pulp in the spleen was noted in the high dose females as well as an increased fiber content in the periportal area of the liver. The adrenal zona

fasciculata of these females exhibited fat vacuoles and a mild reaction of sinus endothelial cells. (NOEL) (M/F): 30 mg/kg/day (based upon the increased spleen weight in the females and increased liver N- and O-demethylase activities in the males of the 100 mg/kg/day treatment group); NOAEL: 300 mg/kg/day; **Study supplemental.** (Moore, 10/11/96)

066; 144990; "HWG 1608: Range-Finding Toxicological Study with NMRI Mice to Establish Dosage for a Chronic Study (Feeding for Eight Weeks) and For Determinations of Enzyme Induction in the Liver (Feeding for Five Days)"; (W. Ramm; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Germany; Study No. 94211; 7/7/86); HWG 1608 (purity: 96.9%) was administered in the diet of 5 mice/sex/group at concentrations of 0, 500, or 2000 ppm for 8 weeks. An additional study was performed in which 5 mice/sex/group were fed the test material for 5 days at concentrations of 0, 125, 500, and 2000 ppm. In the eight week study, livers of the high dose group were enlarged with cell degeneration, necrosis of hepatocytes/vacuole formation and increased fat content in the cells being noted. An increased level of ferriferous pigment was evident in the spleens of the 2000 ppm treatment group. All of these effects except for the necrosis of the hepatocytes and the pigmentation in spleen were noted in the 500 ppm treatment group, as well. In the 5 day feeding study, N-demethylase activity ($p < 0.01$) and cyt. P450 content ($p < 0.05$) were increased in the females of the 125 ppm group. The cyt. P450 content ($p < 0.01$) and the triglyceride levels ($p < 0.01$) were increased in the males of the 125 ppm treatment group. NOEL < 125 ppm (based on induction of liver enzymes and/or increased triglyceride levels in the liver of the 125 ppm treatment group). **Supplemental study.** (Moore, 10/21/96)

068; 144994; "Range-Finding Toxicological Study to Establish Dosage for Subchronic Study of Toxicity to Beagle Dogs"; (E. von Keutz; Bayer AG, Institute of Toxicology, Pharmaceutical, Wuppertal-Elberfeld, Germany; Study No. 94573; 7/1/86); HWG 1608 (purity: 93.4%) was administered in the diet of 2 beagle dogs/sex/group at concentrations of 0, 500 or 5000 ppm for 30 days. No mortality resulted from the treatment. Body weight and food consumption was only minimally affected by the treatment. Serum alkaline phosphatase activity significantly increased in two of the four animals of the high dose group. NOEL (M/F): 500 ppm (based upon increased level of serum alkaline phosphatase activity in the 5000 ppm group). **Supplemental Study.** (Moore, 9/27/96)

** 067; 144992; "Subchronic Study of Toxicity to Dogs with Oral Administration (Thirteen-Week Feeding Study)"; (E. von Keutz; Bayer AG, Institute of Toxicology, FRG; Study No. 94984; 5/6/87); Four dogs/sex/group were administered HWG 1608 (purity: 93.4%) in the diet at concentrations of 0, 200, 1000 or 5000 ppm for 13 weeks (uptake of test material: (M) 0, 8.15, 40.9, 200.7 mg/kg/day, (F) 0, 8.68, 40.6, 216.5 mg/kg/day). One female in the high dose group died on the 2nd day of dosing and was replaced. A treatment-related effect on weight gain was noted with the increase in weight of the high dose males and females being 53 and 61%, respectively, of the control group. Lens opacity of varying intensity and extent was reported in 3 of 8 animals in the 5000 ppm treatment group from week 7 and in all 8 animals by week 10. These lesions were confirmed in the histopathology. Six of the eight animals in the 5000 ppm group exhibited marked anisocytosis after 13 weeks of treatment. The increase in siderosis in the spleen and/or liver as well as a slight weight increase in the spleen of the high dose animals indicated an increased level of blood cell breakdown. An increase in serum alkaline phosphatase activity was noted (maximal level: 5000 ppm (M) 329% of control, week 13, (F) 275% of control, week 7). Liver N-demethylase activity was increased in the 5000 ppm group ((M) 355% of control, (F) 308% of control). The liver cytochrome P450 content increased in the 5000 ppm group as well ((M) 174% of control, (F) 197% of control). Target tissue: eye; **Possible adverse effect:** ocular degeneration; NOEL (M/F): 200 ppm (based upon reduce body weight gain in 1000 ppm treatment group); NOAEL (M/F): 1000 ppm (based upon ocular degeneration in the 5000 ppm treatment group). **Study Acceptable.** (Moore, 10/2/96)

069, 070; 144996, 145005; "21 Day Repeated Dose Dermal Toxicity Study"; (B. Schilde and K.G. Heimann; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Federal Republic

of Germany; Study Nos. 93093, 96759; 5/8/84, 3/3/88); HWG 1608 (purity: 97.1% (Study 1) or 97.4% (Study 2)) was applied dermally to 6 animals/sex/group at doses of 0, 50 or 250 mg/kg/day (Study 1) or to 5 animals/sex/group at doses of 0 or 1000 mg/kg/day (Study 2) for 6 hours/day, 5 days/week for 3 weeks. No treatment-related clinical signs were evident. No treatment-related effects upon hematology, clinical chemistry or urinalysis were noted. No treatment-related lesions were observed. **No adverse effect** indicated at the limit test dose. NOEL (M/F) 1000 mg/kg/day; Study **acceptable**. (Moore, 11/21/96)

071; 145009; "HWG 1608: Study for Subacute Inhalation Toxicity to the Rat for Three Weeks (Exposure 15 x 6 Hours)"; (J. Pauluhn; Bayer AG, Institute of Toxicology, Wuppertal-Elberfeld, Federal Republic of Germany; Study No. 94559; 2/22/85); Ten rats/sex/group were exposed to HWG 1608 (purity: 96.2%) for 6 hours/day, 5 days/week for 3 weeks at reported analytical exposure concentrations of 0, 1.2, 10.6, and 155.8 mg/m³. No treatment-related clinical signs resulted from the exposure. No treatment-related effects upon the hematological, serum chemical or urinalytical parameters were noted. An increase in mean liver N-demethylase activity was noted in the 155.8 mg/m³ group (p<0.01). No treatment-related histopathological lesions were evident. Reported NOEL: (M/F) 10.6 mg/m³ (based upon increased N-demethylase activity in the liver of animals exposed to 155.8 mg/m³ of the test material); reported NOAEL (M/F) 155.8 mg/m³. The analytical data and calculations used to determine the analytical exposure concentrations were not included in the report. The study data will be useful in the health assessment of the test material when this information is provided. **Study Supplemental**. (Moore, 11/25/96)